NASDAQ: AXSM

AXSOME THERAPEUTICS

STRIDE-1 Phase 3 Trial of AXS-05 in TRD

Topline Results

Conference Call

March 30, 2020

AXS-05 in Treatment Resistant Depression (TRD)
STRIDE-1 Phase 3 Trial Topline Results

Introduction	**Mark Jacobson**, Chief Operating Officer
Overview and Summary	**Herriot Tabuteau, MD**, Chief Executive Officer
STRIDE-1 Trial Design & Results	**Cedric O'Gorman, MD**, Senior Vice President, Clinical Development & Medical Affairs
KOL Perspective of STRIDE-1 Data	**Maurizio Fava, MD,** Psychiatrist-in-Chief at Massachusetts General Hospital (MGH), Director of the Division of Clinical Research of the MGH Research Institute, Associate Dean for Clinical & Translational Research at Harvard Medical School
Q&A	**Presenters, Nick Pizzie**, Chief Financial Officer and **Dave Marek,** Chief Commercial Officer
Concluding Remarks	**Herriot Tabuteau, MD**, Chief Executive Officer

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Summary and Overview

Herriot Tabuteau, MD

AXSOME THERAPEUTICS

Chief Executive Officer
Axsome Therapeutics, Inc.

Summary of Topline Results:
Rapid and Significant Effects with AXS-05 in TRD Patients

- AXS-05: a novel, oral, investigational NMDA receptor antagonist with multimodal activity
- Rapid and statistically significant improvements in MADRS versus bupropion at Weeks 1, 2, and overall (key secondary endpoints)
- Numerical separation from bupropion at all timepoints, statistical significance not reached on primary endpoint (Week 6)
- Rapid and highly statistically significant induction of remission on the QIDS-SR-16 (score of ≤ 5) as compared to bupropion starting at Week 1, with significance maintained at every point thereafter
- AXS-05 demonstrated statistically significant improvements in cognitive function and reduction in anxiety symptoms versus bupropion
- AXS-05 was generally safe, well tolerated, and not associated with psychotomimetic effects, weight gain or sexual dysfunction
- These results support continued development in TRD with initiation of second Phase 3 trial anticipated 3Q 2020
- On track for planned NDA filing for Breakthrough Therapy designated AXS-05 in MDD for 4Q 2020

Treatment Resistant Depression (TRD): Urgent Unmet Medical Need

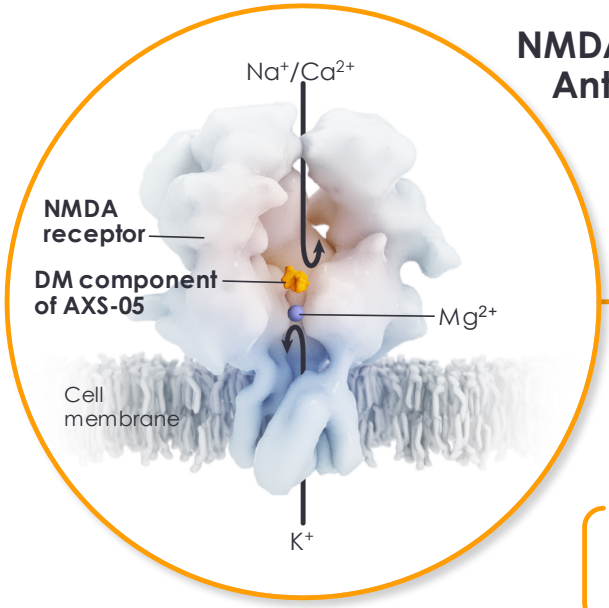
- Depression is a disabling and potentially life-threatening, biologically-based disorder
- 17 million U.S. adults experience major depressive episodes each year and at least one-third of them are considered treatment resistant[1,2]
- Patients are considered treatment resistant if they have not responded adequately to at least 2 different anti-depressants of adequate dose and duration in the current depressive episode[2]
- Treatment resistant depression is a chronic disorder associated with high economic burden, significantly impacted quality of life and various comorbid conditions[3]
- Limited treatment options are available
- Urgent need exists for new treatments that have rapid and significant efficacy, are safe and well tolerated, and offer convenient administration

17 million U.S. adults experience major depressive episodes each year[1]

At least **5.7 million** Of them are considered treatment resistant[2]

1. National Survey on Drug Use and Health (NSDUH). (2017).
2. Rush AJ, et al. *Am J Psychiatry* 2006;163:1905-1917.
3. Mrazek DA et al. *Psychiatr Serv*. 2014;65(8):977-987.

AXS-05: Novel, Oral, NMDA Receptor Antagonist with Multimodal Activity

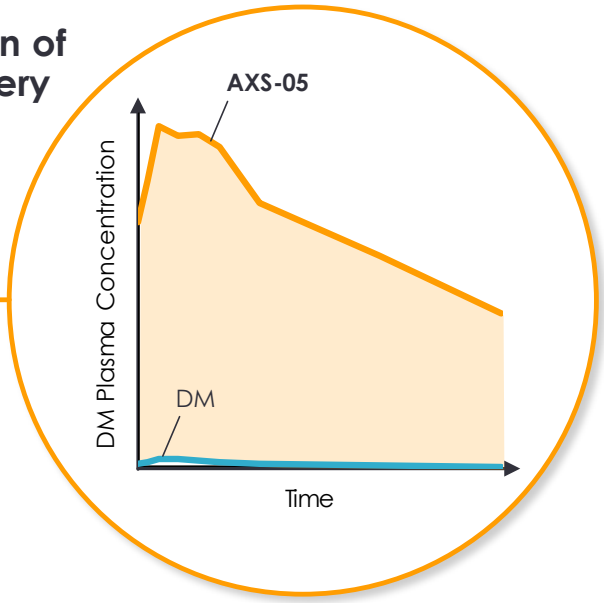


NMDA Receptor Antagonism

AXS-05

dextromethorphan/bupropion **modulated delivery tablet**

Modulation of DM Delivery



Sigma-1 Receptor Agonism

Monoamine Reuptake Inhibition

Abbreviations: DM = Dextromethorphan; Mg2+=magnesium ion; Na+=sodium ion; Ca+2=calcium ion; K+=potassium ion. Axsome data on file

STRIDE-1 Phase 3 Trial Design & Results

Cedric O'Gorman MD, MBA

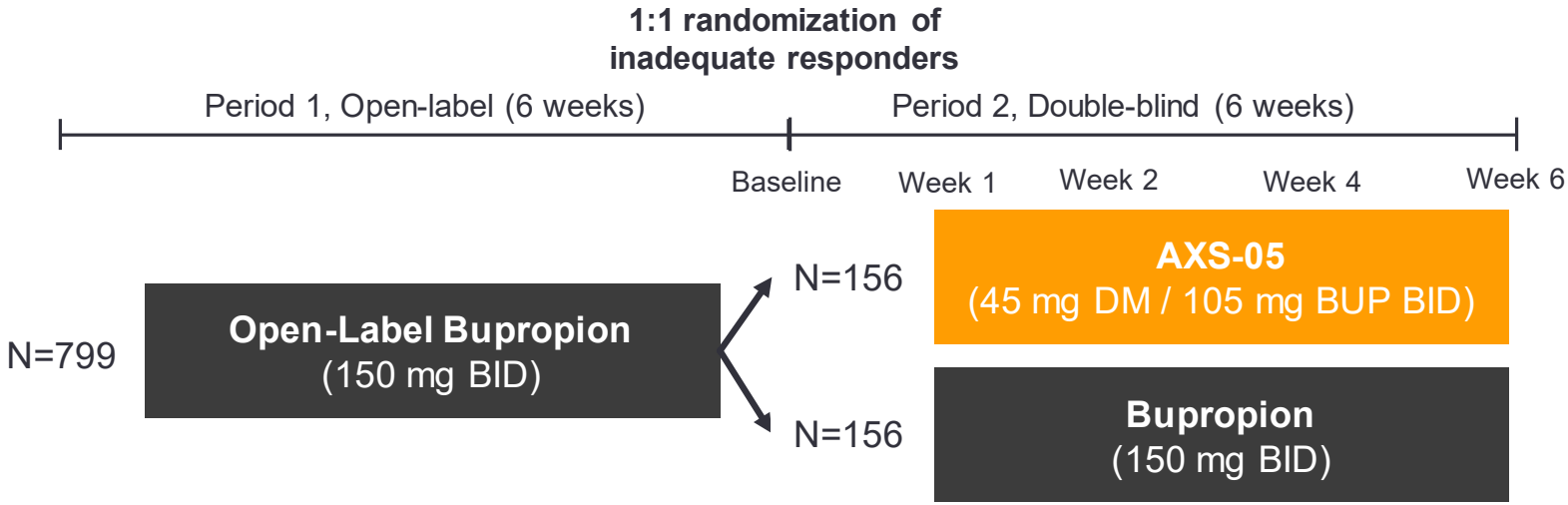
AXSOME THERAPEUTICS

Senior Vice President, Clinical Development and Medical Affairs
Axsome Therapeutics, Inc.

STRIDE-1 Phase 3 Trial: Design Summary

Stride1Study AXS-05

A Phase 3 trial to assess the efficacy and safety of AXS-05 in the treatment of TRD



BID = twice daily; BUP = Bupropion; DM = Dextromethorphan.

- **Primary Endpoint:** Change in depression score from randomization to end of study, measured using the Montgomery-Åsberg Depression Rating Scale (MADRS)

- **Key Secondary Endpoints:**
  - Change from baseline in MADRS at week 2 post-randomization
  - Change from baseline in MADRS at week 1 post-randomization
  - Overall treatment effect on MADRS total score
  - Change from baseline in Sheehan Disability Scale (SDS) at week 6 post-randomization

STRIDE-1 Phase 3 Trial: Key Entry Criteria

Inclusion criteria included:

Open-label Period

- Male or female 18-65 years of age inclusive
- History of inadequate response to 1 or 2 prior antidepressant treatments, established by ATRQ
- Hamilton Depression Rating Scale (HAMD-17) total score of ≥ 18

Double-blind Period

- Inadequate response to 2 or 3 prior antidepressant treatments, including open-label period failure

Exclusion criteria included:

- History of electroconvulsive therapy, vagus nerve stimulation, transcranial magnetic stimulation or any experimental central nervous system treatment during the current episode or in the past 6 months
- Schizophrenia, bipolar disorder, obsessive compulsive disorder
- Psychiatric symptoms secondary to any other general medical condition

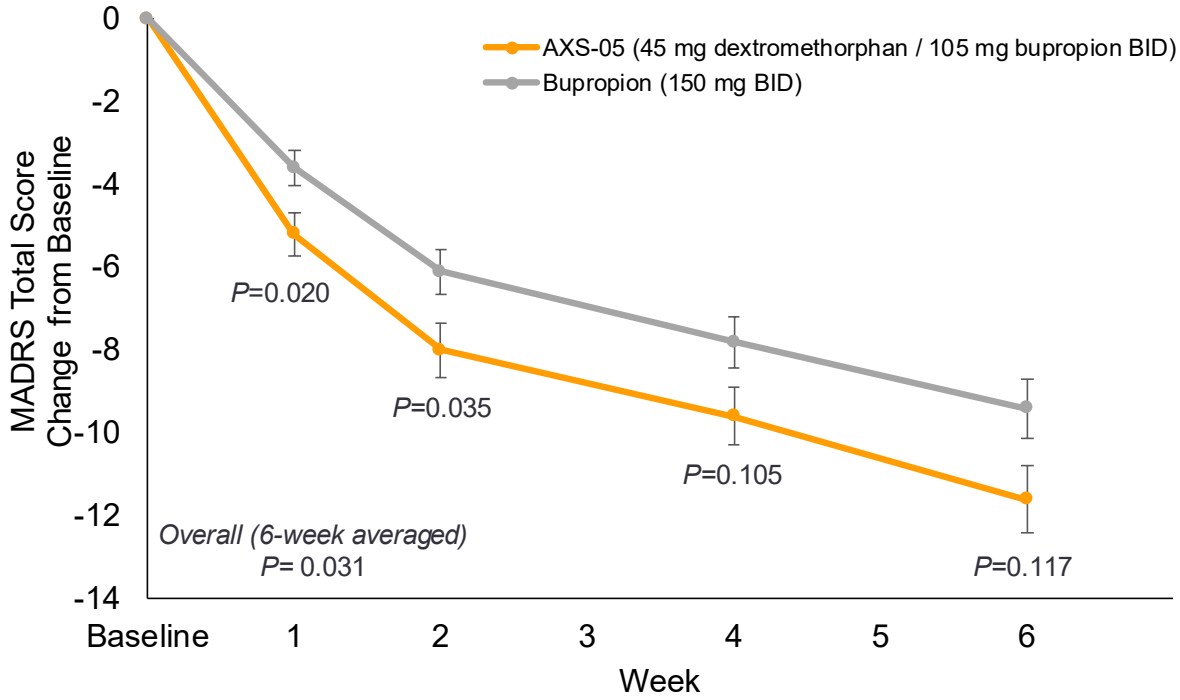
STRIDE-1 Phase 3 Trial:
Demographics and Baseline Characteristics

	AXS-05 (45 mg DM / 105 mg BUP)	Bupropion (150 mg)
Age (years)	44.3 (12.19)	45.1 (12.56)
Female Gender, n (%)	101 (65.6%)	97 (62.6%)
Race, n (%)		
White	100 (64.9%)	106 (68.4%)
Black or African American	41 (26.6%)	39 (25.2%)
Asian	2 (1.3%)	6 (3.9%)
Other or Not Reported	11 (7.1%)	4 (2.6%)
BMI (mg/kg^2)	29.9 (5.85)	29.5 (5.64)
MADRS Total Score	33.4 (5.61)	33.2 (5.17)
CGI-S Score	4.6 (0.61)	4.6 (0.54)

Data are mean (SD) unless otherwise stated.
Abbreviations: BMI = Body Mass Index; BUP = bupropion; CGI-S = Clinical Global Impression – Severity; DM = dextromethorphan; MADRS = Montgomery-Åsberg Depression Rating Scale

- Demographics and baseline characteristics were similar across both treatment groups
- Study completion rates were similar across both treatment groups, 89% for AXS-05 and 94% for bupropion

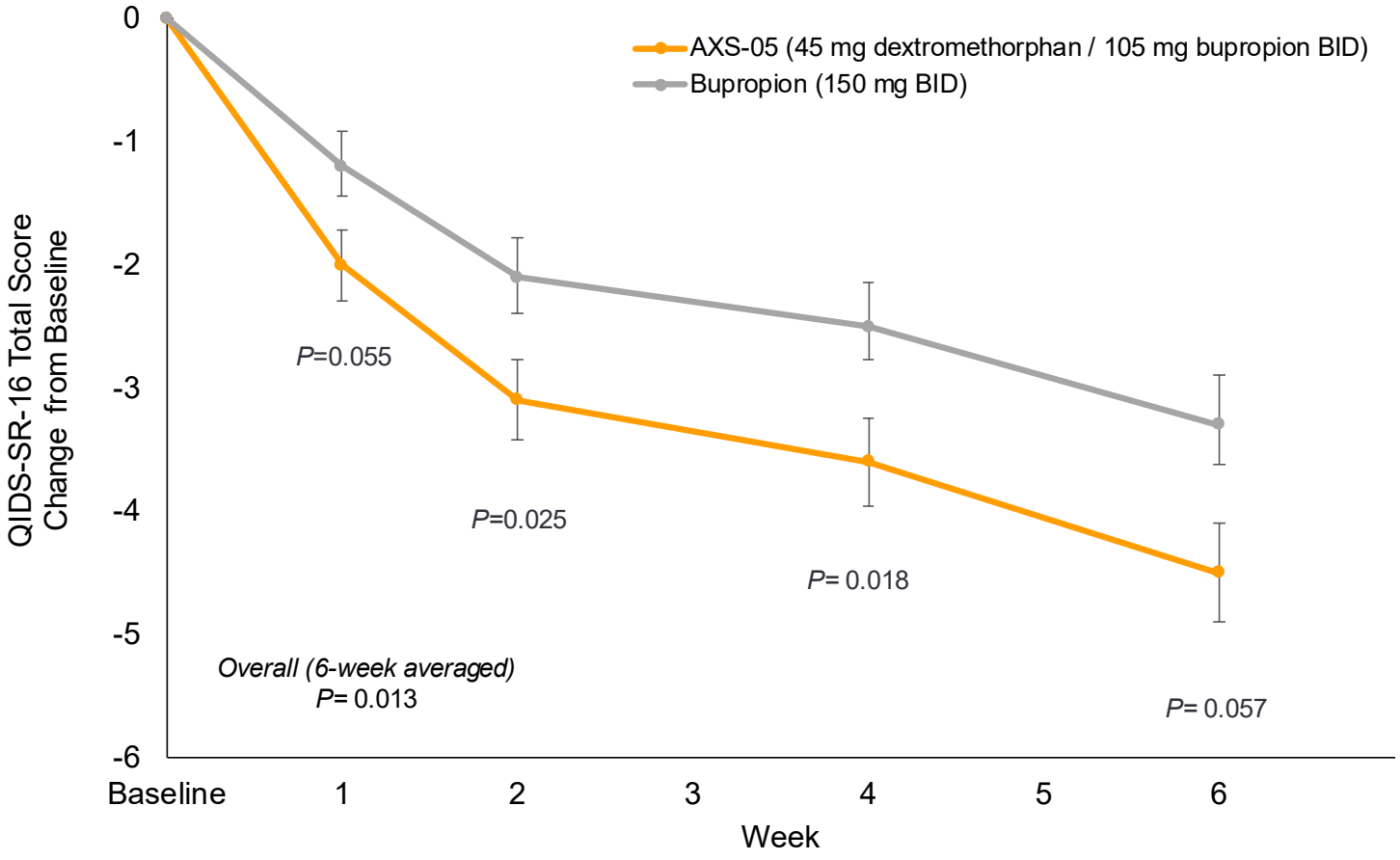
Improvement in Depressive Symptoms: Change in MADRS Total Score



	AXS-05 (n=154)	Bupropion (n=155)	Difference	*P*-Value
Primary Endpoint: Change in MADRS Total Score at Week 6	-11.6	-9.4	-2.2	NS
Key Secondary Endpoints:				
Change in MADRS Total Score at Week 1	-5.2	-3.6	-1.6	0.020
Change in MADRS Total Score at Week 2	-8.0	-6.1	-2.1	0.035
Overall treatment effect on MADRS Total Score	-8.6	-6.7	-1.9	0.031

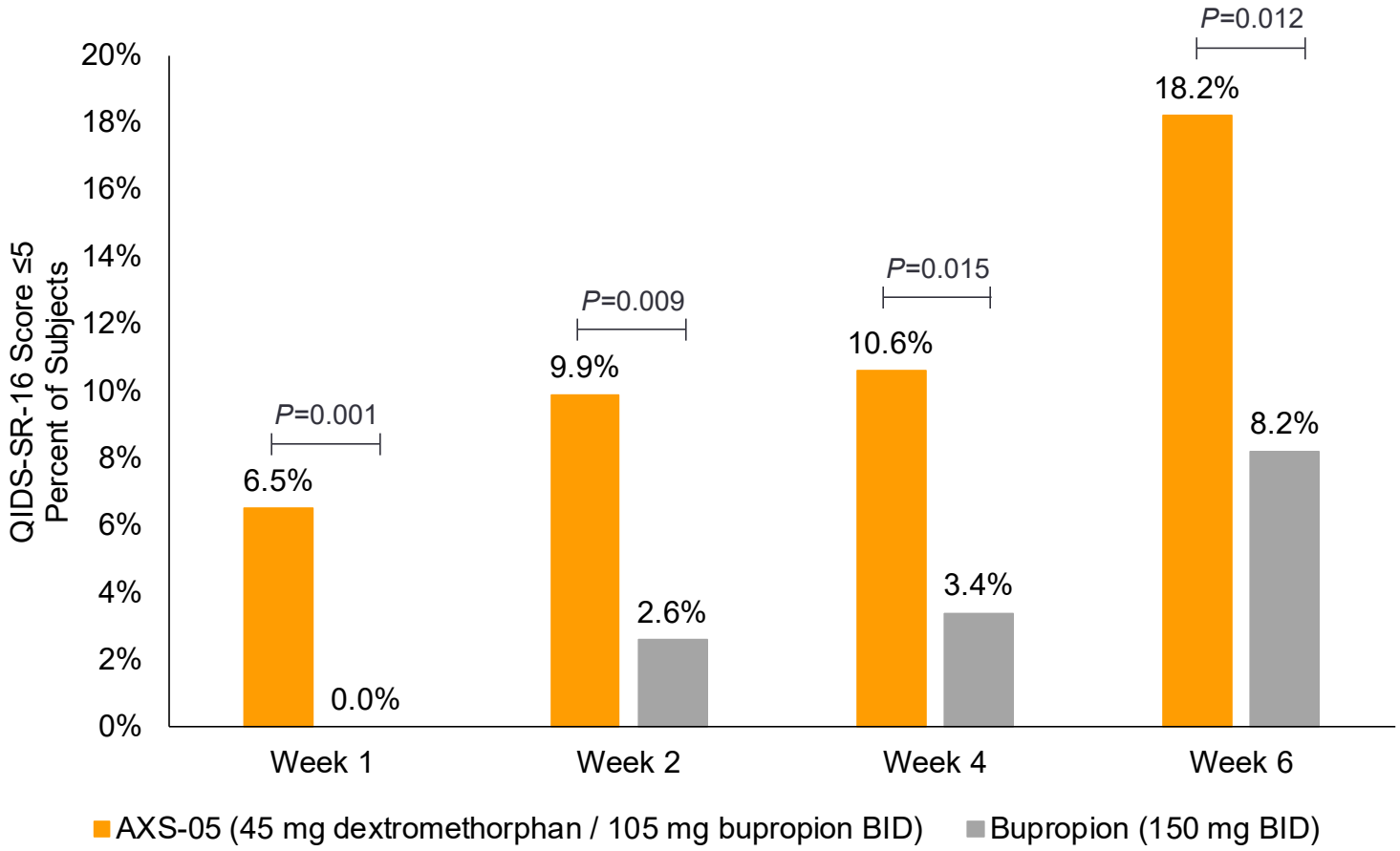
Notes: P-values calculated from LSMean. Abbreviations: BID = twice daily; MADRS = Montgomery-Åsberg Depression Rating Scale

Improvement in Depressive Symptoms: Change in the QIDS-SR-16



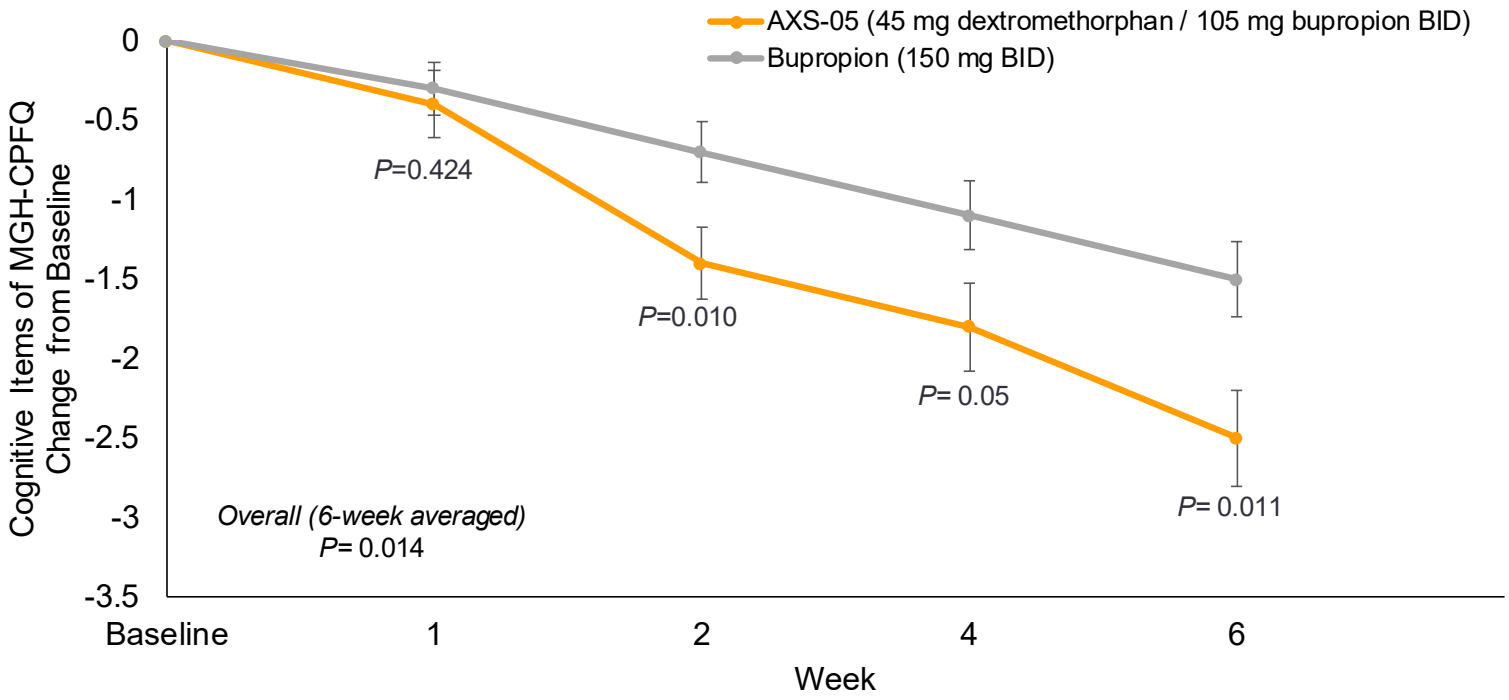
Notes: P-values calculated from LSMean.
Abbreviations: BID = twice daily; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self-Report-16 Item

Improvement in Depressive Symptoms: Achievement of Remission (QIDS-SR ≤ 5)



Notes: P-values calculated from LSMean. Remission cut-off score of ≤5
Abbreviations: BID = twice daily; QIDS-SR-16 = Quick Inventory of Depressive Symptomatology-Self-Report-16 Item

Improvement in Cognitive Function: Change in MGH-CPFQ-Cognitive Dimension



- Cognitive items of the CPFQ assess sharpness/mental acuity, and the ability to focus/maintain attention, to remember/recall information, and to find words
- Each of the 4 items on the cognitive dimension of the CPFQ are scored 1-6, with lower scores representing improvements in cognitive functioning

Notes: P-values calculated from LSMean.
Abbreviations: BID = twice daily; MGH-CPFQ = Massachusetts General Hospital -Cognitive and Physical Functioning Questionnaire

Safety Profile of AXS-05 in TRD: Treatment-Emergent Adverse Events

	Double-blind Period[b]		Open-label Period
	AXS-05 (N = 154)	**Bupropion** (N = 156)	**Bupropion** (n=310)
Any TEAE[a]	**67 (43.5%)**	**61 (39.1%)**	**135 (43.5)**
Dizziness	13 (8.4%)	0	9 (2.9%)
Nausea	8 (5.2%)	3 (1.9%)	22 (7.1%)
Dry mouth	6 (3.9%)	3 (1.9%)	13 (4.2%)
Headache	4 (2.6%)	7 (4.5%)	14 (4.5%)
Insomnia	3 (1.9%)	5 (3.2%)	19 (6.1%)
Constipation	3 (1.9%)	3 (1.9%)	13 (4.2%)
Anxiety	2 (1.3%)	0	11 (3.5%)
Irritability	0	2 (1.3%)	10 (3.2%)

Abbreviations: AE = adverse event. Data presented as number of subjects (% of subjects)

a. Treatment-emergent AEs occurring in ≥3% of subjects during the open-label period or ≥5% of subjects during the double-blind period are reported

b. In double-blind period, treatment-emergent AE is defined as any AE with an onset on or after date of randomization and prior to or on visit 9 date or period 2 early termination date

- Rates of discontinuation due to adverse events were low in both groups; 2.6% for AXS-05 and 1.3% for bupropion
- Three serious adverse events occurred in the AXS-05 arm: migraine, overdose, and suicidal ideation (8 days after subject completed treatment)

STRIDE-1 Phase 3 Trial Results: Summary

- AXS-05 met key secondary endpoints by rapidly improving symptoms of depression in patients with treatment resistant depression (TRD)
- AXS-05 demonstrated numerical improvement on primary endpoint (MADRS at Week 6) versus active comparator, but did not reach statistical significance
- Statistically significant greater rates of remission on the QIDS as compared to bupropion
- Statistically significant improvements with AXS-05 compared to bupropion in cognition and anxiety
- AXS-05 was generally safe and well tolerated in this trial, consistent with our prior experience with AXS-05

KOL Perspective on STRIDE-1 Data

Professor Maurizio Fava, MD

AXSOME THERAPEUTICS

Psychiatrist-in-Chief at Massachusetts General Hospital (MGH)

Director of the Division of Clinical Research of the MGH Research Institute

Associate Dean for Clinical & Translational Research at Harvard Medical School

Q&A

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Concluding Remarks

Herriot Tabuteau, MD

Chief Executive Officer
Axsome Therapeutics, Inc.

AXS-05: Clinical Programs in Psychiatry

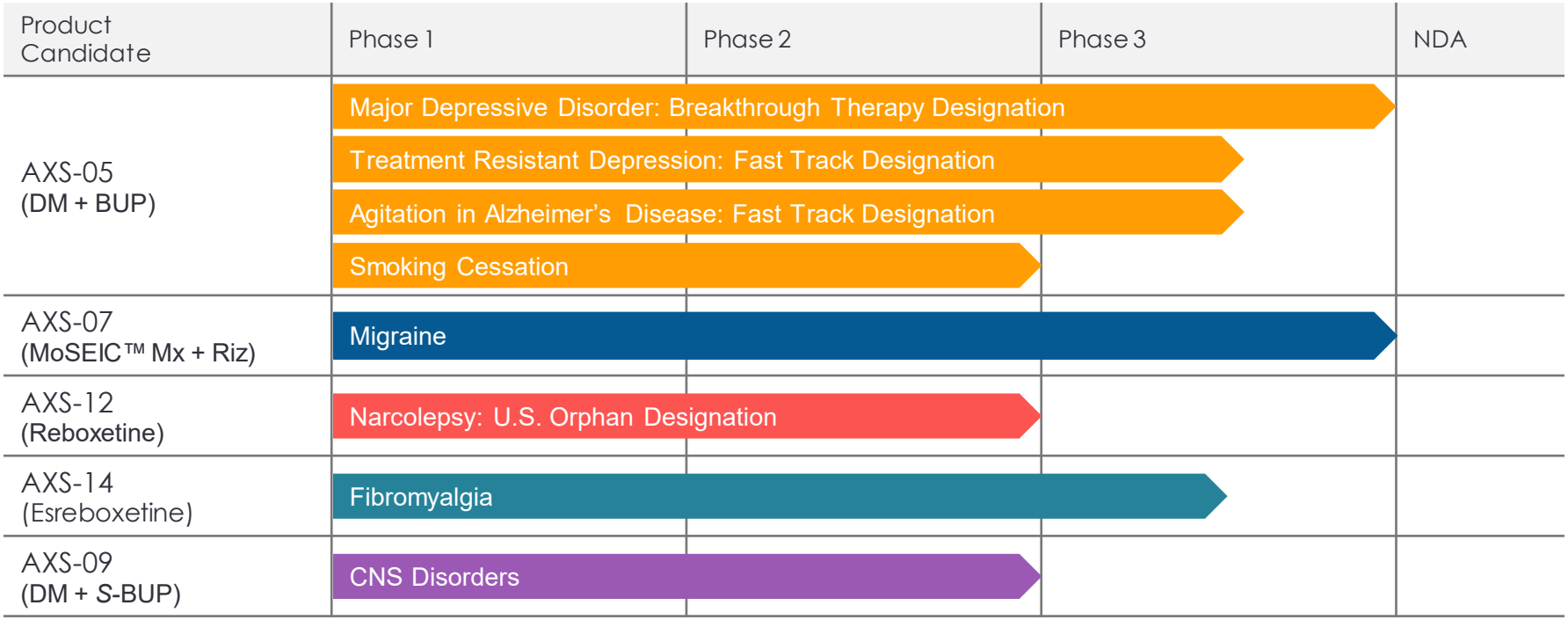
	Clinical Program				
	ASCEND	**GEMINI**	**STRIDE-1**	**AXS-05 / OL**	**ADVANCE-1**
Indication	MDD	MDD	TRD	MDD/TRD	AD Agitation
Phase	Pivotal Phase 2	Pivotal Phase 3	Pivotal Phase 3	Open-label Phase 3	Pivotal Phase 2/3
Objectives	Efficacy of AXS-05 vs. BUP	Efficacy of AXS-05 vs. PBO	Efficacy of AXS-05 vs. BUP	Long-term safety of AXS-05	Efficacy of AXS-05 vs. BUP and PBO
Status	Completed	Completed	Completed	Ongoing	Dosing Complete
Subjects Dosed	96	326	310	876	>360

Abbreviations: BUP = bupropion; MDD = Major Depressive Disorder; OL = Open-label; PBO = placebo; TRD = Treatment Resistant Depression

- NDA filing of AXS-05 in the treatment of MDD, based on positive results from GEMINI and ASCEND trials on track for 4Q 2020
- FDA Breakthrough Therapy designation granted in MDD, Fast Track designation in TRD and AD agitation

Our CNS Candidates and Pipeline

- Five differentiated clinical-stage CNS assets targeting significant and growing markets
- Patent protection to 2034-2036, worldwide rights for most product candidates



Abbreviations: BUP = Bupropion; CNS = Central Nervous System; DM = Dextromethorphan; Mx = Meloxicam; Riz = Rizatriptan; S-BUP = Esbupropion.

Our Clinical and Regulatory Milestones

Product Candidate	Indication	2020
AXS-05 (DM + BUP)	**MDD**	● **NDA** submission (4Q)
	TRD	● **STRIDE-1** topline results
	AD Agitation	● **ADVANCE-1** Phase 2/3 topline results (early 2Q)
	Smoking Cessation	● **FDA** meeting (2020)
AXS-07 (MoSEIC™ Mx + Riz)	**Migraine**	● **INTERCEPT** Phase 3 topline results (imminent) ● **NDA** submission (4Q)
AXS-12 (Reboxetine)	**Narcolepsy**	● **Phase 3** trial start (2020)
AXS-14 (Esreboxetine)	**Fibromyalgia**	● **FDA** meeting (2020)

Abbreviations: AD = Alzheimer's Disease; BUP = Bupropion; DM = Dextromethorphan; MDD = Major Depressive Disorder; Mx = Meloxicam; Riz = Rizatriptan; TRD = Treatment Resistant Depression.

✓ Accomplished milestone.

● Upcoming milestone.

AXSOME THERAPEUTICS

Thank you.

For more information, please contact

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